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Stickel, Felix ; Z'graggen, Kaspar

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Short title: Bevacizumab for Osler's disease

Felix Stickel[1,2], Kaspar Z'graggen[3]

[1]Hepatology Unit, Hirslanden Clinic Beau-Site, Bern
&
[2]Department of Gastroenterology and Hepatology, University Hospital of Zürich, Switzerland
[3]Centre of Visceral Surgery, Clinic Beau-Site Hirslanden, Bern

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Abbreviations used in the text: HCC, hepatocellular carcinoma; HHT, hereditary hemorrhagic teleangiectasia; LT, liver transplantation; VM, vascular malformation

Corresponding author
Felix Stickel, MD
Hepatology Unit
Hirslanden Clinic Beau-Site
Schänzlihalde 11, 3013 Bern
Switzerland
Tel: +41 31 335 7817; Fax: +41 31 335 3519
felix.stickel@uzh.ch; felix.stickel@hirslanden.ch

Ethics

No ethics committee approval has been obtained for this study since the report represents a single patient experience. However, written informed consent from the patient according to the Journal's guidelines has been retrieved in which the patient approves publication of data anonymously.

To the Editor,

Three reports recently presented clinical data and comments on a 65-year old woman in whom hereditary haemorrhagic teleangiectasia (HHT; Osler's disease) and hepatocellular carcinoma (HCC) coincided, leading to listing for liver transplantation (LT) (1-3). Consensus existed on the usefulness of LT in patients with HHT, particularly when complicated by HCC, but there was debate over the right timing for LT in such patients who are usually well besides the complications of vascular malformations (VM). The reported case was complicated by the fact that trans-arterial chemoembolization for HCC is contraindicated in HHT due to a high incidence of abscesses. Hence, therapeutic interventions that override the transplant list waiting time are needed.

Dubuis-Girod and Buscarini (3) advocate the use of bevacizumab, an endothelial growth factor antibody approved for treating various cancers, as a "bridge-to-transplant" measure in patients with HHT and hepatic VM according to a trial in which 20/24 patients with HHT responded to bevacizumab with improvements of cardiac index (CI), nose bleeds, and quality of life (4).

We report on a 72-year old female with HHT and VM (type III) with symptoms of high cardiac output, bilateral leg edema, palpitations and cardiac cachexia with a weight loss of 7kg/11 months. We started bevacizumab treatment 3 years ago at 5mg/kg for 6 applications every other week. Treatment was then very well tolerated and all symptoms subsided. Cardiac output (CO) decreased from 15.3L/min (CI 9.5L/min/m^2) to 7.0L/min (4.4L/min/m^2), and further improved to 6.5L/min (3.9L/min/m^2) 2½ years after treatment cessation.

However, the patient recently complained about similar symptoms as initially, and CO and CI were measured at 9.0L/min and 5.5L/min/m^2, respectively. We started a second course with bevacizumab (5mg/kg) during which the patient developed acute

abdominal pain and presented with fever at 39.2°C, leucocytosis 12.100/L, C-reactive protein 126mg/L and mild cholestasis. Computed tomography excluded intestinal perforation, but showed bilateral intrahepatic portal vein thrombosis (**figure 1**). Upon analgesia, ceftriaxone and nadroparin symptoms improved rapidly, and treatment with phenprocoumon was started.

Our case confirms that bevacizumab can markedly improve cardiac symptoms and function in patients with HHT and offers treatment for those not eligible for LT. However, bevacizumab may cause serious side effects among which deep vein thrombosis has been reported in up to 13% of treated patients in oncology trials (5). Although thromboembolic events could predominantly be due to the underlying malignancy (6), they should be carefully considered when treating patients with HHT for which bevacizumab is not officially approved and for which experience is still limited to case series.

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Legend to

Figure 1

CT scan showing bilateral portal vein thrombosis (white arrows).